

**REMARKS**

Reconsideration and withdrawal of the rejections set forth in the Office action dated April 24, 2003 re respectfully requested. Applicants petition the Commissioner for a one-month extension of time in which to file this amendment. A separate petition is enclosed.

**I. Amendment**

Claim 1 is amended to recite that the method is directed to administering a compound to a person suffering from a multi-drug resistant neoplastic condition, as set forth on page 6, lines 24-26.

Claims 8 and 12 are amended to correct a typographical error.

New claims 22 and 23 are directed to the embodiment shown in Fig. 3F and described on page 15, line 2-13, where the hydrophilic polymer chain carrying the folate ligand has a greater molecular weight than polymer chains with no ligand.

**II. Rejections under 35 U.S.C. §102**

Claims 1-2 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Mislick *et al.* (*Bioconjugate Chem.*, 6:512-515 (1995)).

Claims 1-2, 4-14, and 16-21 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Lee *et al.* (*Biochimica et Biophysica Acta*, 1233:134-144 (1995)).

Claims 1-2, 4-14, and 16-21 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Goren *et al.* (*Proceed. Intl. Symp. Control Rel. Bioact. Mater.*, 24:865-866 (1997)) or Horowitz *et al.* (Chemistry and Biology of Pteridines and Folates, Pfleiderer and Rokos, eds., 11<sup>th</sup> Symposium, p. 353-356 Berlin, 1997).

Claims 1-3 and 13-15 were rejected under 35 U.S.C. §102(a) as allegedly anticipated by Brasier (U.S. Patent No. 5,804,445).

These rejections are respectfully traversed for the following reasons.

Summaries of Applicants' invention and of the cited documents are provided in the response submitted August 30, 2001.

A. Rejection Over Mislick

1. Legal Standard for Novelty

To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either expressly or inherently. M.P.E.P. § 2131.

2. Examiner's Position

The Examiner asserts that Mislick destroys the novelty of the present claims since Mislick teaches delivery of DNA to carcinoma cells by means of a folate-polylysine DNA complex.

3. Applicants' Position

The present claims are directed to a method of administering a therapeutic agent to a subject suffering from a multi-drug resistant neoplastic condition (claim 1) and to a method of administering to a subject suffering from a multi-drug resistant neoplastic condition that includes one or more cells in which a therapeutic compound in free form does not accumulate (claim 9).

As noted above, Mislick teaches administering DNA to carcinoma cells via a polylysine-folate complex. There is no teaching in Mislick of administration of an agent to a multi-drug resistant cell. Thus, the Examiner's rejection over Mislick necessarily assumes that such carcinoma cells are multi-drug resistant cells, since this is the only way that all the claim elements could be found in the teaching. It is unclear to Applicants how the Examiner makes this leap, from carcinoma cells to multi-drug resistant cells, since not all carcinoma cells are drug resistant, let alone multi-drug resistant. Mislick nowhere teaches that carcinoma cells are multi-drug resistant cells. Without some basis for making the necessary assumption, the present rejection cannot stand, since Mislick nowhere teaches the claimed element of administering a therapeutic compound to a subject suffering from a multi-drug resistant neoplastic condition.. Nor does Mislick show that administering a therapeutic compound via the folate receptor permits accumulation of the compound in the multi-drug resistant cells of the neoplasm.

Accordingly, Mislick does not anticipate the present claims, and withdrawal of the rejection is respectfully requested.

**B. Rejection over Lee et al.**

Lee et al. disclose folate-targeted liposomes for delivery of doxorubicin to epithelial tumor cells.

The Examiner finds this teaching to destroy novelty of the present claims. Since there is no teaching or suggestion in Lee et al. of administration of a folate-targeted drug conjugate to a multi-drug resistant cell, the Examiner must be assuming that epithelial tumor cells are multi-drug resistant cells. Indeed this is not the case, since not all tumor cells are drug resistant, let alone multi-drug resistant. Without some teaching in Lee et al. of a multi-drug resistant cell, or some basis for supporting the assumption that epithelial tumor cells are multi-drug resistant cells, the rejection cannot stand. Withdrawal is respectfully requested.

**C. Rejection over Goren et al. or Horowitz et al.**

Goren et al. pertain to folate-targeted liposomes for the delivery of doxorubicin to single agent resistant tumor cells. There is no teaching or suggestion in Goren et al. of a method of administering an agent to a multi-drug resistant cell. Again, the Examiner necessarily assumes that the tumor cells of Goren et al. are associated with a multi-drug resistant neoplastic condition. This is not shown in Goren et al., nor is this assumption supported by knowledge in the art since not all tumor cells are multi-drug resistant.

Accordingly, the rejection over Goren et al. fails and withdrawal is respectfully requested.

Horowitz et al. relate to folate-targeted liposomes for delivery to single agent resistant tumor cells. Horowitz et al. fail to teach or suggest a method of administering an agent to a multi-drug resistant cell. The arguments noted above for Goren et al. are applicable to Horowitz et al. There is no basis for supporting the necessary assumption that tumor cells are by definition multi-drug resistant cells.

Accordingly, the rejection over Horowitz et al. fails and withdrawal is respectfully requested.

**D. Rejection over Brasier**

Brasier relates to treatment of asthma by administration of a polypeptide. In one embodiment the polypeptide is given in combination with a folate-conjugated liposome. Brasier nowhere shows or suggests a method of administering an agent to a multi-drug resistant cell.

Again, the Examiner necessarily assumes that because Brasier teaches a folate-targeted liposomes, there is a teaching of a multi-drug resistant neoplastic condition. This is not shown in Brasier as this reference nowhere mentions multi-drug resistant cells.

Accordingly, the rejection over Brasier fails and withdrawal is respectfully requested.

In summary, Applicants submit that the present claims are not anticipated by the cited documents, and respectfully request withdrawal of the rejections under 35 U.S.C. §102.

**III. Rejections under 35 U.S.C. §103**

Claims 1-2, 4-14, and 16-21 were rejected under 35 U.S.C. §103 as allegedly obvious over Lee *et al.* or Goren *et al.* or Horowitz *et al.*

Claims 1-3, and 13-16 were rejected under 35 U.S.C. §103 as allegedly obvious over Mislick *et al.* or Brasier in view of Lee *et al.* or Goren *et al.* or Horowitz *et al.* individually or in combination.

These rejections are respectfully traversed.

**A. Analysis**

To establish a *prima facie* case of obviousness, the prior art references (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143.

As discussed above, Applicants' claims relate to a method of administering an agent to a subject suffering from a multi-drug resistant neoplastic condition. The cited documents fail to show or suggest a method of administering an agent to multi-drug resistant neoplastic condition.

With respect to the rejection over Lee *et al.* or Goren *et al.* or Horowitz *et al.*, these references are silent on the problem of multi-drug resistance, and nowhere suggest a method for administering an agent to a multi-drug resistant cell or a means to accumulate an agent in such a cell.

The same arguments apply to the rejection over Mislick *et al.* or Brasier, in view of Lee *et al.* or Goren *et al.* or Horowitz *et al.* Namely, none of the references either alone or in combination show or suggest a method for administering an agent to a multi-drug resistant cell or for achieving accumulation of an agent in such a cell.

Accordingly, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §103.

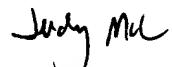
IV. CONCLUSION

In view of the above remarks, Applicants submit that the claims now pending are in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

The Examiner is invited to contact Applicants' representative at 650-838-4402 if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted,

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